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# Conservative evolution and industrial metabolism in Green Chemistry†

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To date, chemistry has provided more than a hundred million new compounds, most of which are non-natural species that have never existed before and are a source of an enormous amount of pollution. With the increased amount of these “man-made” chemicals being synthesised and environmental concerns of chemical processes, chemists have become very aware of these potential risks and dangers. As an answer to this challenge, Green Chemistry emerged and brought with it a list of necessary measures to be followed in the laboratory that has been gradually completed. Herein, we present evidence for the manifestation of two related principles within Green Chemistry: (i) *conservative evolution*, which refers to the observation that throughout the history of the universe, old construction blocks, such as elementary particles, amino acids, or living cells remained conserved while the world evolved in its complexity, and (ii) the practice of *industrial metabolism* that is a manifestation of conservative evolution in human activity referring to the application of biological metabolism in the production of goods for our civilization. Related concepts of Green Chemistry, such as the atom economy, as a metric of green chemistry, the application of safer chemicals and solvents, the utilization of catalysis, the utilization of renewable resources, and *in situ* spectroscopy, are discussed, providing examples to students and researchers from academy to industry involving the work of Professor István T. Horváth.

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†This paper is dedicated to Professor István T. Horváth on the occasion of his 65th birthday.

## Introduction

Evolution can be defined as a process that leads to an increased and viable complexity.<sup>1</sup> By accepting this definition, it can be definitely stated that humans, as part of the bio-



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sphere, also contribute to evolution by creating new constructions involving processes and materials synthesized using chemical methods. Today, millions of products in the chemical industry, such as transportation fuels, fertilizers, polymers and composites, pharmaceuticals, detergents, food additives, dyes, agrochemicals, *etc.*, are in widespread use, maintaining, or even increasing, the living standards of our society. So far, more than 130 million artificial chemical substances have been produced, which have previously not existed in Nature. In addition, this production is highly based on fossilized carbon resources, *i.e.* crude oil, natural gas, and coal, making our society fossil fuel dependent. While this number continuously increases by *ca.* 1 million per year, limited information is available on the impact of new compounds on living organisms and the environment. By releasing these compounds into the biosphere, these materials could interact with natural substances and a very small portion may be embedded in existing living systems without harm. The rest has to be considered as more or less toxic, threatening life, which is manifested in the harmful interaction of xenobiotics with biomolecules. Moreover, several serious environmental and health problems have been caused by chemicals over the last 50 years. For example, chemical disasters have occurred in Seveso (Italy, 1976)<sup>2</sup> and Bhopal (India, 1985),<sup>3</sup> and the large scale utilization of hazardous substances such as DDT (1940–1970),<sup>4</sup> chlorofluorocarbons (1960s–1994),<sup>5,6</sup> or the direct use of chiral substances such as thalidomide on humans (1960s),<sup>7</sup> just to name a few, have resulted in global and/or local issues, which have directed the attention of researchers towards the development of environmentally friendly methodologies for the synthesis of new chemicals and the use of less harmful substances.

The evolution of Green Chemistry, as a collection of guiding concepts, can be considered as one of the first responses for these purposes, focusing on materials and processes that could operate in harmony with Nature and minimize their risk on the environment.<sup>8,9</sup> Although it is indeed hard to apply all of the principles of Green Chemistry together at the same time, the more of them that result in the realization of alternative processes, the more that environmentally benign processes can be realized.<sup>9</sup>

As an analogy to biological metabolism, that involves the elimination of superfluous substances from an organism, industrial metabolism was born as a concept, and realizes the importance of material and energy integration and the turnover of industrial systems.<sup>10</sup> Therefore, a generalization of industrial metabolism is a concept of a circular economy, representing a regenerative system, where resource input and waste and emissions, as well as energy leakage, are minimized by optimizing materials and energy loops.<sup>11</sup>

The concept of conservative evolution refers to the observation that during the history of the universe only new construction blocks survived, which were based on ones that already existed.<sup>12</sup> The proton, the neutron and the electron appeared very early after the Big Bang and these particles conserved their properties and have been the basic constituents of

molecular matter up until the very present. A variety of different molecules was formed and though these can be decomposed under specific conditions, some of them conserved their role over billions of years. The most important groups are amino and nucleic acids, which have been the basic molecular building blocks of living systems for more than three billion years. Water has a specific role in life as a safe and very effective solvent. Thus, the vast majority of biochemical processes take place in an aqueous environment and this has not changed since the first living cell appeared on Earth. Furthermore, cells, though differentiated into dozens of forms, have remained the basic constituents of living systems throughout the history of life. Catalysis plays a fundamental role in the efficient transformation of molecules and energy production in living organisms. Life has evolved through the harmonious utilization of renewable resources and treatment of waste. Lots of further examples can be given for the manifestation of conservative evolution. Consequently, the adaption of these fundamental observations could lead to the establishment of greener and cleaner chemical processes.

Herein, we call attention to the chemical substances and processes that play a key role in the twelve principles of Green Chemistry representing conservative evolution and/or industrial metabolism.<sup>8</sup> Our examples primarily refer to the work of Professor István T. Horváth, whose contribution to this field is spectacular.

## Results and discussion

### The atom economy

The manifestation of industrial metabolism can be exemplified by the second principle of Green Chemistry. As Barry M. Trost has proposed, synthetic methods should be designed to maximize the incorporation of all atoms used in the reaction into the final product, which allows the minimization or even elimination of useless or harmful wastes.<sup>13</sup> Atom economy can be considered an excellent “green metrics” of transformations at the molecular level and it is able to define a reaction to be “green”. However, process chemistry usually needs auxiliary substances to assist in the establishment of conditions for a 100% atom economic reaction. Therefore, environmental aspects should be subsequently evaluated by the fate of auxiliary substances after the isolation and purification of the product(s). For this purpose, Sheldon introduced the Environmental factor (E-factor)<sup>14</sup> as a metric applicable for the assessment of the performance of a complete production process. Recently, it has been generally accepted and used by the chemical industry. The E-factor is defined as the mass ratio of waste to the desired product. Both the E-factor and atom economy are strongly related to the greenness of a chemical process from the laboratory to industrial scale and represent widely accepted measures of the environmental impact of such processes. Here we provide some representative examples of reactions exhibiting 100% atom economy.



It goes without saying that addition reactions are excellent examples of transformations representing 100% atom economy. One of the earliest papers by Váradý, Horváth, and Pályi *et al.* described the conversion of carbon monoxide and acetylene to bifurandiones, which can be considered as attractive compounds to the polymer industry. The  $\text{Co}_2(\text{CO})_8$ -catalyzed reaction represents 100% atom economy; however, the efficiency of the transformation is rather low, indicated by only a 4–6% product yield (Scheme 1).<sup>15</sup> It was shown that the addition of tertiary trialkylphosphines or trialkylphosphites resulted in a considerable improvement in the yields, reaching 30–72% depending on the type of alkyl substituents present on the phosphorous ligand. A yield of 72% was achieved by conversion of acetylene and CO in the presence of  $\text{P}(n\text{Bu})_3$  at 120 °C.<sup>16</sup>

Several addition reactions can be considered as a part of “click-chemistry”, which represents a powerful and highly reliable tool for the synthesis of useful organic, and usually biologically active, compounds.<sup>17</sup> Since the seminal papers by Sharpless<sup>18</sup> and Meldal,<sup>19</sup> highly regioselective copper-catalyzed azide–alkyne cyclo-addition (Cu-AAC, Scheme 2) has received significant interest as a novel synthetic methodology. Accordingly, several improvements were made in order to increase the efficiency of the reaction and to widen its applicability. Heaney *et al.* reported a simplified protocol to obtain 1,2,3-triazoles using an alkynylcopper(i) polymeric precatalyst without the necessity of the addition of a ligand in a microwave-assisted reaction at 100 °C.<sup>20</sup> Díez-González showed that commercially available  $\text{CuBr}(\text{PPh}_3)_3$  acts as a catalyst for the preparation of diverse 1,2,3-triazoles in a strict click reaction. The catalyst operates at room temperature and at a low

(50 ppm–0.5 mol%) catalyst loading, resulting in the formation of triazoles in generally high (>85%) yields. It is worth noting that this system also allowed “neat” conditions to be used.<sup>21</sup> The Cu-AAC mediated addition of acetylene to both aliphatic and aromatic azides to form the corresponding 1-substituted-1,2,3-triazoles was demonstrated by Liang. The reactions were carried out in the presence of triethylamine as a base in DMSO under 1 bar of acetylene at room temperature<sup>22</sup> and the isolated yields were between 86–97% depending on the type of azide used. Lim applied  $\beta$ -cyclodextrin as a phase transfer catalyst for the preparation of 1,2,3-triazoles with excellent yields (90–99%) in water, as an environmentally benign reaction medium, at room temperature, which is a useful protocol from both an economic (*e.g.* using a cheap  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  catalytic precursor) and an environmental point of view, as well as for the practical convenience of not having to handle flammable anhydrous organic solvents, and toxic and expensive reagents.<sup>23</sup>

Polymerization reactions were used to produce more than 300 million tons of materials in 2014 worldwide and assist in the everyday life of human society, from plastic bags, clothing, and cutlery, automobiles to healthcare, and electronics and smart materials and they are also excellent examples of 100% atom economy. The mechanism of the transition metal-catalyzed polymerization of ethylene (or another olefin), which has a distinguished role in polymer chemistry, starts by the coordination of the  $\text{C}=\text{C}$  bond to the activated metal center of the metallocene catalyst and followed by the insertion of a co-ordinated olefin into the metal–carbon bond of the growing polymer chain. According to the Cossee–Arman mechanism, a  $\beta$ -migratory insertion step, taking place *via* an intermediate alkyl-olefin complex, was proposed. However, its presence was not detected until 1990, when the first observation of Co-alkyl complexes in the  $[\text{C}_5\text{Me}_5(\text{P}(\text{OMe})_3)_3\text{CoCH}_2\text{CH}_2-\mu\text{H}]^+$ -catalyzed polymerization of ethylene was reported by Brookhart and Horváth *et al.* A pioneering *in situ* high-pressure NMR study using  $^{13}\text{C}$ -labelled ethylene evidenced the existence of these complexes and clearly established the chain growing mechanism (Scheme 3).<sup>24</sup> A similar study was reported in collaboration with Prof. Nozaki revealing the mechanism of the alternating copolymerization of propylene with carbon monoxide in the presence of a Pt-(*R,S*)-BINAPHOS catalyst. It was shown that the *cis/trans* isomerization from (*SP*-4-4)-[Pt( $\text{CH}_3$ )(CO)((*R,S*)-BINAPHOS)] [B(3,5-( $\text{CF}_3$ )<sub>2</sub> $\text{C}_6\text{H}_3$ )<sub>4</sub>] to the more stable *SP*-4-3 isomer is faster than the formation of its acyl derivatives *via*



Scheme 1 Synthesis of bifurandiones.



Scheme 2 Azide–alkyne cycloaddition (Cu-AAC).



Scheme 3 Mechanism of the polymerization of ethylene. Adapted with permission from ref. 24. Copyright of the American Chemical Society (1990).



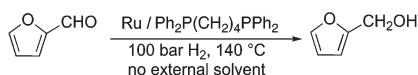
CO insertion. For the Pd-(*R,S*)-BINAPHOS-catalyzed copolymerization, there exist at least two major resting states, most probably the acyl palladium species,  $(SP-4-3)\text{-[Pd(C(=O)R)((R,S)\text{-BINAPHOS})(L^2)]}[B(3,5\text{-(CF}_3)_2C_6H_3)_4]$  ( $L^2 = CH_3CN, CO$ ), and the alkyl palladium species,  $[Pd\{CH_2CH(CH_3)C(=O)R\}((R,S)\text{-BINAPHOS})][B(3,5\text{-(CF}_3)_2C_6H_3)_4]$ .<sup>25</sup>

Selective hydrogenation reactions can also exemplify atom economic processes. Among these transformations, the conversion of an initial platform chemical furfural (FAL)<sup>26</sup> to furfuryl alcohol (FOL) is one of the most industrially important hydrogenation reactions. It takes place in either the liquid or gas phase in the presence of a highly toxic copper-chromite catalyst on a large scale.<sup>27</sup> Therefore, in order to reduce the environmental risk of this transformation, several attempts have been made to develop alternative catalyst systems.<sup>28</sup> Recently it was shown that a Ru/Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>4</sub>PPh<sub>2</sub> catalyst was able to convert FAL to FOL in the absence of any external solvent or other auxiliary materials, opening up an environmental friendly route (Scheme 4) to this reaction. The catalyst was found to be recyclable over twelve consecutive runs without any decrease in its activity and selectivity.<sup>29</sup>

The oxidation of ethylene to ethylene oxide is also an important reaction in the large-scale chemical industry. The original reaction, the so-called “chlorohydrin process” exhibited several serious environmental concerns including the loss of chlorine gas that was used in the formation of calcium chloride and the generation of unwanted chlorine-containing by-products. Since the discovery of a heterogeneous Ag-based catalyst by Lefort in 1931 that allows the direct oxidation of ethylene to ethylene oxide, the manufacturing process has theoretically become a 100% atom economic process (Scheme 5); however, the practical selectivity of the industrial-scale process is between 80–90% depending on the type of catalyst system used, *i.e.* the type of solid support used, the presence of promoters, *etc.* It should be noted that no other metal has been found that can compete with Ag for this purpose.

### Safer chemicals

According to the fourth principle of Green Chemistry, chemical products should be designed to affect their desired function while minimizing their toxicity. This is again a manifestation of the principle of industrial metabolism.



**Scheme 4** Selective hydrogenation of FAL to FOL.



**Scheme 5** Oxidation of ethylene to ethylene oxide.

One of the excellent examples of a safer chemical is  $\gamma$ -valerolactone (GVL), which was first proposed as a sustainable liquid for the production of energy and carbon-based chemicals by Horváth in 2008.<sup>30</sup> This compound is a component of fruit and it is frequently used as a food additive. It is a liquid in the temperature range of  $-31$ – $207$  °C, has a high open cup flash point ( $96$  °C), a definite smell, low toxicity ( $LD_{50, rat} = 8800$  mg kg<sup>-1</sup>)<sup>30</sup> and is fully miscible with water, assisting biodegradation. It is important to note that GVL does not form any measurable amount of peroxides under air in weeks,<sup>31</sup> contrary to the behaviour of 2-methyltetrahydrofuran (2Me-THF) or ethers, *e.g.* diisopropyl-ether, making it a rather safe compound for large scale use. GVL has a low vapor pressure, preventing its emission into the environment, and can be separated from water and alcohols, without the formation of an azeotropic mixture.<sup>32,33</sup> The multistep conversion of biomass from sucrose to alkanes involving the synthesis of GVL was first demonstrated by Horváth's group in 2008.<sup>34</sup> Obviously, the most effective protocol to synthesize GVL is the selective hydrogenation of levulinic acid in the presence of a catalyst. Reduction leads to the formation of 4-hydroxyvaleric acid, which readily undergoes ring closure to form GVL. For this purpose, external solvent-free methods were developed, including the transfer hydrogenation protocol.<sup>35–37</sup> Since GVL was proposed as a platform molecule, several innovative applications have been demonstrated, opening up a renewable-based route to produce carbon-based chemicals. It can be reduced to form 1,4-pentanediol and 2Me-THF by a tertiary phosphine, *e.g.* P(*n*Bu)<sub>3</sub>,<sup>34</sup> P(*n*Oct)<sub>3</sub>, or a triphos (C(CH<sub>3</sub>)P(CH<sub>2</sub>PPh<sub>2</sub>)<sub>3</sub>)-modified Ru-based catalyst system.<sup>37</sup> It should be noted that 2Me-THF can be subsequently reduced in the presence of a Pt-based catalyst to form olefins and alkanes.<sup>34</sup> GVL can be converted to butenes by its decarboxylation in the presence of a SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst, and can then be oligomerized to form industrially important higher olefins.<sup>38,39</sup> As Horváth proposed, GVL could be a replacement for fossil-based hydrocarbons in igniting and lighter fluids, as well.<sup>40</sup> Alkoxyvalerates and valerate-based ionic liquids, which could be considered and used as partially bio-ionic liquids, can also easily be obtained from GVL.<sup>41,42</sup> Their applications as reaction media for hydrogenation reactions involving transfer hydrogenation protocol<sup>42,43</sup> and Ullmann-type cross-coupling reactions<sup>44</sup> were recently demonstrated. Biomass-based polymer precursors such as hydroxyamides can also be easily synthesized by the ring-opening of GVL under mild conditions.<sup>45</sup> Moreover, the synthesis of dimethyl adipate or adipic acid from GVL could open up alternative routes as a feedstock for the Nylon industry.<sup>46</sup> Since optically-active lactones occur naturally and can be used as chiral building blocks for the synthesis of biologically active compounds, GVL has been proposed as a chiral biomass-based building block.<sup>47</sup> A summary of GVL-based chemicals is presented in Scheme 6.

Dimethyl carbonate (DMC), the simplest organic carbonate, has an important role in the chemical industry and moreover, its low toxicity ( $LD_{50, rat} = 13\,000$  mg kg<sup>-1</sup>)<sup>48</sup> for human health and other life forms makes it a safe, non-corrosive green







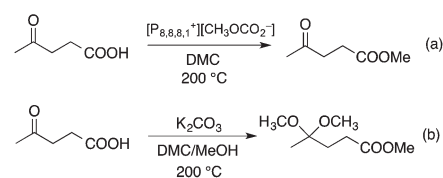
**Scheme 6** GVL-based chemicals.

chemical for sustainable processes. The conventional production of DMC is based on the reaction of methanol with highly toxic phosgene using a chlorinated solvent. The first phosgene-free alternative process was based on the oxidative carbonylation of methanol in the presence of Cu(I)-chloride. However, due to the formation of wet HCl by the hydrolysis of the chloride containing Cu-species, the process is extremely corrosive and all of the commercial equipment exposed to the CuCl–MeOH–H<sub>2</sub>O–HCl mixture must therefore be glass-lined. Furthermore, the formation of chlorinated organic side-products could also result in an environmental issue. Because the catalyst precursor is the only source of chlorine in the system, application of a chlorine-free catalyst overcomes the drawbacks of the process. Horváth and Mehnert *et al.* developed a chlorine free-catalyst, which is prepared *in situ* from Cu(II)-acetate and 2,2'-bipyrimidine for the oxidative carbonylation of methanol (Scheme 7), which was investigated under both batch and semi-continuous conditions.<sup>49</sup> *In situ* high-pressure IR and NMR spectroscopic studies suggested the formation of [Cu(2,2'-bipyrimidine)(CO)(OMe)] as one of the key intermediates. The catalytic performance of the novel catalyst system was found to be similar to the CuCl-based one under identical conditions. The chlorine-free catalyst was immobilized by copolymerizing 5-vinyl-2,2'-bipyrimidine with styrene.<sup>49</sup>

DMC is a safe, non-corrosive, and environmentally friendly alternative building block for carbonylating, carboxymethylating and methylating agents, phosgene, methoxycarbonyl chloride, dimethyl sulfate, and methyl halides, respectively.<sup>50–53</sup> Recently, DMC has been introduced as an alkylating agent in the conversion of platform chemicals obtained from renewable feedstocks or biomass-based waste streams. Perosa's group investigated the reaction of levulinic acid (LA) with DMC in the presence of a different catalyst.



**Scheme 7** Oxidative carbonylation of methanol to dimethyl carbonate.



**Scheme 8** Alkylation reactions of levulinic acid with dimethyl carbonate.

Complete conversion of LA and an exceptional yield of methyl levulinate (96%) was detected by using a 20-fold excess of DMC and [P<sub>8.8.8.1</sub>][CH<sub>3</sub>OCO<sub>2</sub>] as a base/catalyst at 200 °C for 6 h (Scheme 8). By addition of methanol as a co-solvent, the formation of the dimethyl-ketal of methyl levulinate in the presence of K<sub>2</sub>CO<sub>3</sub> was detected.<sup>54</sup> The same group demonstrated that cinnamyl alcohol and 4-(3-hydroxypropyl)phenol, the two compounds resembling the lignin building block *p*-coumaryl alcohol, could be selectively converted by catalytic methodologies based on DMC as the green reagent (Scheme 9). It was revealed that selectivity of the catalytic



**Scheme 9** Alkylation of cinnamyl alcohol and 4-(3-hydroxypropyl)phenol with DMC. Adapted from ref. 55 with permission from the Royal Society of Chemistry.

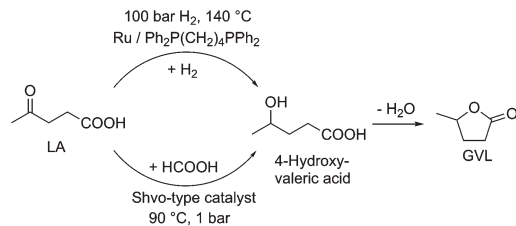


system could be tuned by changing the reaction temperature and the nature of the catalyst. While basic catalysts, *e.g.*  $\text{K}_2\text{CO}_3$ ,  $[\text{P}_{8,8,8,1}][\text{CH}_3\text{OCO}_2]$  ( $[\text{P}_{8,8,8,1}]$ : a trioctyl methylphosphonium cation) and  $\text{CsF}/\text{Al}_2\text{O}_3$  promote transesterification reactions at lower temperatures (*ca.* 90 °C), amphoteric solids, such as alkali-metal exchanged faujasites, selectively accelerate the formation of alkyl ethers at higher temperatures (165–180 °C).<sup>55</sup> As an extension of this study, the bis-*O* methylation of 1,2- and 1,4-dihydroxybenzene derivatives, which can also be found in the product spectrum of lignin depolymerization to the corresponding bis-methyl ethers, was investigated in the temperature range of 100–170 °C using microwave irradiation as a heating method. Both stoichiometric as well as catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were effective for bis-methylation at relatively mild temperatures. An almost quantitative conversion of catechol and hydroquinone toward the corresponding bis-methylated products were achieved in excellent isolated yields at 170 °C.<sup>56</sup>

### Safer solvents

Solvents are an intrinsic part of many chemical reactions and “solvent-friendly chemical thinking” has evolved due to many advantages in both laboratory and industrial operations, including the simple regulation of temperatures (reflux), moderation of exothermic reactions, dissolution of solids to get molecules into a common phase, facilitation of mixing, lowering of viscosity and density, *etc.* Although “external solvent-free” transformations could offer environmental friendly solutions, in reality, many thousands, if not millions of chemical reactions, can only operate in liquid media. As an outcome, the industrial activities involving solvents result in the release of volatile organic compounds (VOCs), including conventional solvents, into the environment. For example, for the EU28 alone, over 6 million tons of VOC are released annually,<sup>57</sup> some of which are leading to serious environmental concerns. Consequently, the elimination or replacement of conventional organic solvents with environmentally benign or even biomass-based alternatives with a low vapor pressure, low or no toxicity, low flammability and a limited negative impact on the environment is a crucial part of the development of greener and cleaner chemical technologies.

Obviously, the complete elimination of solvent(s) as auxiliary material(s) from reactions could result in an ideal “external solvent-free” or so-called “neat” reaction condition offering the best solution for the solvent issue. When one of the substrates is liquid under reaction conditions, it also acts as an “internal solvent”. Consequently, the term “solvent-free” cannot be stated for these cases and the use of the term “external solvent (s)-free” has to be preferred. In addition, the composition of the reaction environment continuously changes from the substrate(s) to product(s) during the reaction. This can easily be demonstrated by the “neat” hydrogenation of LA to 4-hydroxyvaleric acid (4-HVA) in the presence of a catalyst *in situ* generated from  $\text{Ru}(\text{acac})_3$  and  $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$  (Scheme 10).<sup>34,35,37</sup> At the beginning of the reaction, 100% of LA is present as a solvent and at the end of the conversion  $\text{GVL}:\text{water} = 1:1$



**Scheme 10** External solvent-free (neat) hydrogenation of LA to 4-hydroxyvaleric acid.

(n/n) has to be considered as the reaction medium. It should also be noted that the transfer hydrogenation of LA by the use of  $\text{HCOOH}$  can also be carried out under “neat” conditions (Scheme 10) resulting in a mixture of GVL,  $\text{H}_2\text{O}$ , and  $\text{HCOOH}$ . This elegant approach was reported by Horváth in 2014.<sup>36</sup>

Although “neat” transformations could offer environmentally friendly alternatives, most reactions can only be operated in the presence of solvents. Because chemical reactions take place under aqueous conditions in living organisms, there is no doubt that *water* could be an excellent reaction medium as a readily available, cheap, nonflammable and nontoxic liquid. Water is one of the basic and irreplaceable components of living systems and other solvents, especially VOCs, seem to not be able to compete with its evolutionary advantages. Accordingly, several efforts have been made to develop catalytic systems that operate in water, of which organic analogues have been well-known for a long time. An outstanding example is the aqueous Ruhrchemie/Rhône-Poulenc biphasic hydroformylation process of propylene in the presence of  $\text{HRh}(\text{CO})(\text{TPPTS})_3$  (TPPTS: the sodium salt of *m*-trisulfonated-triphenylphosphine).<sup>58</sup> The process was developed for the hydroformylation of propylene to butanal and the ratio of normal- to iso-butanal is about 25, which is surprisingly high compared with that used in the conventional triphenylphosphine-modified ( $\text{HRh}(\text{CO})(\text{PPh}_3)_3$ ) hydroformylation system under similar conditions. It was proposed that the coordination of the olefin to the coordinatively unsaturated  $\{\text{HRh}(\text{CO})(\text{phosphine})_2\}$  or  $\{\text{HRh}(\text{CO})_2(\text{phosphine})\}$  species results in a high or low normal- to iso-butanal ratio, respectively. A pioneering high-pressure *in situ* NMR study by Horváth and co-workers established that only  $\text{HRh}(\text{CO})(\text{TPPTS})_3$  was detectable in water even under high syngas ( $\text{CO}:\text{H}_2 = 1:1$ ) pressures of up to 200 bar (Fig. 1). In the case of  $\text{PPh}_3$ , only the presence of the known species  $\text{HRh}(\text{CO})_2(\text{PPh}_3)_2$  was observed at a low (30 bar,  $\text{CO}:\text{H}_2 = 1:1$ ) syngas pressure making the coordinatively unsaturated  $\text{HRh}(\text{CO})_2(\text{PPh}_3)$  species easily accessible for the olefin. The activation energy of the dissociation of TPPTS from  $\text{HRh}(\text{CO})(\text{TPPTS})_3$  was found to be significantly higher,  $11 \pm 1 \text{ kcal mol}^{-1}$ , than that of the dissociation of  $\text{PPh}_3$  from  $\text{HRh}(\text{CO})(\text{PPh}_3)_3$ .<sup>59</sup> The higher activation energy of the dissociation of TPPTS from  $\text{HRh}(\text{CO})(\text{TPPTS})_3$  was attributed to the intramolecular association of  $-\text{SO}_3^-$  of the neighboring TPPTS ligands *via* hydrogen bonding in aqueous medium, representing one of the first examples of outer sphere control.



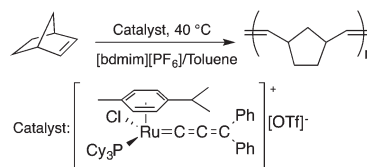


**Fig. 1**  $^{13}\text{C}$  NMR (a) and  $^{31}\text{P}$  NMR (b) spectra of  $\text{HRh}(^{13}\text{CO})(\text{TPPTS})_3$  in the presence of a 3 molar excess of TPPTS under a 200 bar pressure of  $^{13}\text{CO} : \text{H}_2 = 1 : 1$  in  $\text{D}_2\text{O}$ . Modified with permission from ref. 59. Copyright of Springer (1989).

Ionic liquids (ILs) have attracted considerable attention as alternative reaction media for a huge variety of chemical transformations, due to their extremely low vapor pressure, good solvating properties, reasonable thermal stability, and easily tunable chemical (*e.g.* acidity, basicity, and polarity) and physical properties (*e.g.* viscosity, melting point or vapor pressure).<sup>60–62</sup> However, few applications of ILs as reaction media have been realized on an industrial scale. While a huge variety of ILs have been utilized on a small laboratory scale, the large scale application of an ionic liquid was realized during an investigation of the mechanism of a well-known Beckmann-rearrangement reaction of cyclohexanone oxime to  $\epsilon$ -caprolactam in  $\text{H}_2\text{SO}_4$  or  $\text{H}_2\text{S}_2\text{O}_7$ .<sup>63</sup> Horváth first recognized that the industrially applied “rearrangement mixture”, used by all  $\epsilon$ -caprolactam manufacturers, is actually a  $\epsilon$ -caprolactamium hydrogen cation with a  $\text{HSO}_4^-$  and/or  $\text{HS}_2\text{O}_7^-$  anion (Scheme 11) depending on the presence of sulfur trioxide. It is important to note that formation of an  $\epsilon$ -caprolactamium-type ionic liquid that could hold  $\text{SO}_3$  very strongly up to 140 °C results in a very low vapor pressure of the reaction environment providing safer conditions for this very exothermic reaction. The first ring-opening metathesis polymerization of norbornene as a cyclic olefin in the ionic liquid  $[\text{bdmim}][\text{PF}_6]$  (1-butyl-2,3-dimethylimidazolium hexafluorophosphate) in the presence of the cationic ruthenium allenylidene precatalyst  $[(p\text{-cymene})\text{RuCl}(\text{PCy}_3)(=\text{C}=\text{C}=\text{CPh}_2)][\text{OTf}]$  was reported by Horváth and Dixneuf *et al.*<sup>64</sup> When norbornene was reacted in  $[\text{bdmim}][\text{PF}_6]$ , a 98% polymer yield was isolated after its extraction with toluene and precipitation using methanol. However, the catalyst activity decreased after recycling the catalyst containing the IL, presumably due to either decomposition or removal of the catalyst. By applying a  $[\text{bdmim}][\text{PF}_6]$ -toluene biphasic system to assist in the *in situ* extraction of the polymer, excellent yields (>96%) were obtained over three con-



**Scheme 11** Formation of  $\epsilon$ -caprolactamium-type ionic liquids.



**Scheme 12** Ring-opening metathesis polymerization of norbornene. Adapted from ref. 64 with permission from the Centre National de la Recherche Scientifique (CNRS) and the Royal Society of Chemistry.

secutive runs (Scheme 12). Although several examples of rare-earth-mediated organic reactions in ILs have been described, the first reaction involving cerium(IV)-salts in IL was reported by Horváth and Binnemans in 2007 (Scheme 13).<sup>65</sup> The  $\text{Ce}(\text{IV})$ -mediated oxidation of benzyl alcohol as a model reaction was demonstrated in 1-ethyl-3-methylimidazolium triflate  $[\text{C}_2\text{mim}][\text{TfO}]$ . It was found that the selectivity of the reaction of cerium(IV)-triflate with benzyl alcohol in dry ionic liquids depended on the degree of hydration of the cerium(IV)-triflate as follows: anhydrous cerium(IV) triflate transforms benzyl alcohol into dibenzyl ether, whereas hydrated cerium(IV) triflate afforded benzaldehyde as the main reaction product. Investigation of the oxidation of a series of benzyl alcohol derivatives in a temperature range of 100–125 °C showed that an increase in the reaction temperature leads not only to a faster reaction but also to a higher selectivity toward the desired product. Quantitative conversion of 5-hydroxymethylfurfural (5-HMF) to 2,5-furandicarboxaldehyde and 1,4-hydroquinone to 1,4-quinone were also achieved at 100 °C and room temperature, respectively.<sup>65</sup> Recent developments in the chemistry of ionic liquids, including their characterization, synthesis, and applications, were reviewed in a themed issue of Chemical Reviews in 2017.<sup>66</sup>

Bioliquids derived from a renewable feedstock represent a novel replacement for conventional organic solvents in well-established chemical transformations. Although some of them, *i.e.* ethanol, have been well-known as reaction media for a long time, the characterization of new candidates and possible applications have come into the focus of interest and have been the subject of recent research. GVL was first proposed as a biomass-based solvent by Horváth in 2008.<sup>66</sup> Because it is an aprotic and dipolar molecule, it can dissolve several types of substrates and catalysts. However, some limiting factors have to be considered *e.g.* (i) the presence of water in GVL results in the formation of 4-HVA, which could be a reactant in unwanted side reactions, and (ii) at higher temperatures the thermal stability of GVL is a limiting factor for its applicability. Despite

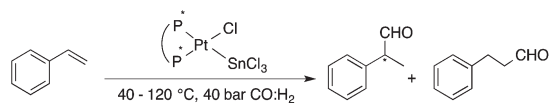


**Scheme 13** Oxidation of benzyl alcohol and its derivatives.

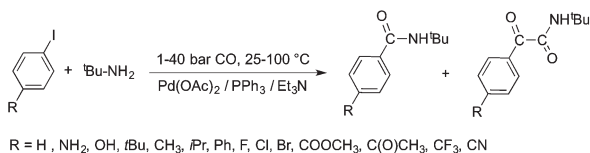


**Scheme 14** Conversion of D-fructose to GVL in GVL.

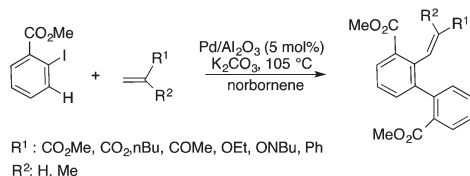
these drawbacks, several successful applications for both homogeneous and heterogeneous catalysis have already been demonstrated. Horváth used GVL as a reaction medium for the acid-catalyzed conversion of fructose to levulinic acid and its subsequent selective reduction *via* a transfer hydrogenation reaction to 4-hydroxyvaleric acid using a Shvo-type catalyst (Scheme 14). The  $^{13}\text{C}_5$ -GVL derived from  $^{13}\text{C}_6$ -fructose with an overall yield of 55% and the GVL solvent was distinguished with ease using a  $^{13}\text{C}$ -labelling technique. GVL can also be successfully utilized as a reaction medium for the homogeneous Pt- (Scheme 15) and Rh-catalyzed enantioselective hydroformylation of styrene,<sup>67,68</sup> as well as the Pd-catalyzed aminocarbonylation (Scheme 16) of iodoaromatic compounds.<sup>69</sup> In general, slightly lower activities were observed in GVL compared to in conventional organic solvents, however, the selectivities were similar, allowing its application as an alternative reaction environment. For heterogeneous catalysis, Vaccaro and co-workers demonstrated that synthetically important coupling reactions such as the Heck,<sup>70</sup> Sonogashira,<sup>71</sup> Hiyama,<sup>72</sup> and Catellani-reactions (Scheme 17)<sup>73</sup> could be suc-



**Scheme 15** Enantioselective hydroformylation of styrene in GVL.



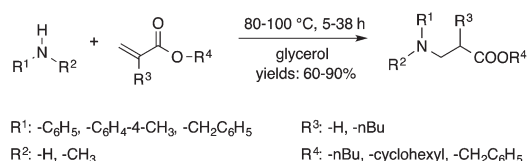
**Scheme 16** Aminocarbonylation of iodobenzene and its derivatives in GVL.



**Scheme 17** The Catellani reaction in GVL.

cessfully performed in GVL. The same group investigated C–H arylation reactions, which were accomplished with a user-friendly heterogeneous palladium catalyst in GVL. The protocol was characterized by an ample substrate scope and high functional group tolerance in the C–H arylation of 1,2,3-triazoles, and the palladium catalyst could be recycled and reused in the process.<sup>74</sup>

Glycerol is a readily available, biodegradable, and environmentally benign solvent obtained as a by-product of the large-scale transesterification of a triglyceride in the production of natural fatty acid derivatives on an industrial scale. Its toxicity (LD<sub>50, rat</sub> = 12 600 mg kg<sup>−1</sup>)<sup>75</sup> is much lower than that of methanol (LD<sub>50, rat</sub> = 5600 mg kg<sup>−1</sup>)<sup>76</sup> or ethanol (LD<sub>50, rat</sub> = 7000 mg kg<sup>−1</sup>).<sup>77</sup> In addition, the increasing demand for biodiesel fuel production also results in it being produced in an increased amount. However, the production of solvent quality glycerol requires high-energy consuming purification processes. Wolfson first reported the application of glycerol as a reaction medium for the Baker's Yeast catalyzed asymmetric reduction of ketones under mild conditions. From a series of stoichiometric organic transformations, Jérôme and co-workers demonstrated that the aza-Michael reaction of *p*-anisidine and butyl acrylate as a model reaction can be performed at 100 °C.<sup>78</sup> While over 80% yield was obtained in glycerol, in water and conventional organic solvents such as toluene, dimethylsulfoxide (DMSO) or DMF less than 5% and zero conversions were detected, respectively. Substrate screening revealed that both electron donating and withdrawing groups were tolerated resulting in product yields of between 60–90% (Scheme 18). The addition of indol and its derivatives to β-nitrostyrene also proceeded under similar conditions. Deligeorgiev reported on an environmentally benign, microwave-assisted procedure for the synthesis of substituted 2-cyanomethyl-4-phenylthiazoles from 2-bromoacetophenones in glycerol (Scheme 19). Excellent yields were obtained over very short (3.5–4.5 min) reaction times and the products were also isolated with very high purity. This approach can be applied to the preparation of a variety of 2-cyanomethyl-4-phenylthiazoles.<sup>79</sup> Glycerol has also received increased interest as a reac-



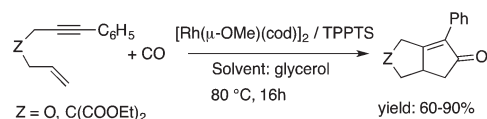
**Scheme 18** Aza-Michael reactions in glycerol.



**Scheme 19** Synthesis of substituted 2-cyanomethyl-4-phenylthiazoles.







**Scheme 20** The Rh-catalyzed Pauson–Khand carbocyclization of enynes.

tion medium for transition metal catalyzed reactions. Gómez and co-workers demonstrated the efficient Rh-catalyzed Pauson–Khand carbocyclizations of 1,6-enynes to bicyclo[3.3.0]octenones in neat glycerol. Interestingly, the reaction can be performed by  $[\text{Rh}(\mu\text{-OMe})(\text{cod})]_2$  in the absence of any ligand under an atmospheric CO pressure at 80 °C (Scheme 20). However, TPPTS can enhance the catalyst performance at low Rh/TPPTS (1 : 1 or 1 : 2) ratios.<sup>80</sup> It should be noted that no or negligible activities were detected in toluene or tetrahydrofuran as reference organic solvents. The catalytic activity associated with  $[\text{Rh}(\mu\text{-OMe})(\text{cod})]_2$  is in contrast to the lack of activity observed with the chlorine-bridged  $[\text{Rh}(\mu\text{-Cl})(\text{cod})]_2$ , which can be attributed to the Brønsted-basic character of the methoxide group in a protic medium such as glycerol. Glycerol has been proposed as an ideal alternative to isopropanol as both hydrogen source and solvent in transfer hydrogenation reactions. Crotti showed that organoiridium derivatives of the type  $\text{Ir}(\text{diene})(\text{N-N})\text{X}$  (diene: 1,5-hexadiene or 1,5-cyclooctadiene; N–N = 2,2'-bipyridine, 1,10-phenanthroline and its substituted derivatives; X = Cl, I) in the presence of a base, such as  $\text{K}_2\text{CO}_3$ , was able to catalyze the hydrogen transfer reaction from glycerol to acetophenone, yielding dihydroxyacetone and phenylethanol in a temperature range of 100–120 °C.<sup>81</sup> At the same time, Wolfson and co-workers demonstrated the activity of  $[\text{RuCl}(\mu\text{-Cl})(\mu^6\text{-}p\text{-cymene})]_2$  in the reduction of benzaldehyde to benzyl alcohol, using KOH or NaOH as bases, with a yield of 99%.<sup>82</sup> When ultrasonic (US) conditions were applied, the catalyst loading and reaction time could be reduced to 1 mol% and 3 h, respectively. Both Ir(II) and Ir(III) complexes bearing N-heterocyclic carbene (NHC) ligands also showed catalytic activity in the transfer hydrogenation reactions of various aldehydes to the corresponding alcohols in glycerol. The catalytic behaviour of Ir complexes was explored under microwave (MW) irradiation and US conditions allowing significant reduction in the catalyst loading and reaction time from 15–24 h to 0.5–1 h.<sup>83,84</sup> Beyond these selected examples, several solvent applications of glycerol, for example in the reduction of nitroarenes and nitriles, in Heck and Sonogashira coupling, in Suzuki reactions, in the enantioselective reduction of aromatic ketones, in the acid catalyzed dehydration of fructose, *etc.*, have also been demonstrated.<sup>85–87</sup>

Lactic acid and its esters are cheap and readily available bio-based solvents and can be industrially produced on a large scale by fermentation. Lactic acid has been used for the first time to promote organic reactions, such as the three-component reactions of styrenes, formaldehyde and an active phenol derivative (Scheme 21). The three-component reactions

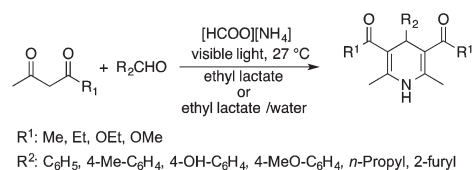


**Scheme 21** Three component reaction in lactic acid.

of diethyl acetylenedicarboxylate, anilines and aromatic aldehydes, aniline-catalyzed condensations between salicylaldehydes and diethyl acetylenedicarboxylate, and the synthesis of substituted quinolines through the Friedländer reaction between 2'-aminoacetophenone and 1,3-dicarbonyl compounds resulting in excellent yields in several cases have also been demonstrated.<sup>88</sup> Ligand-free Pd-catalyzed Suzuki–Miyaura cross coupling reactions have been performed in a tunable solvent system comprising water and ethyl lactate (Scheme 22). The protocol tolerated the reactions of several substituted aryl halides and aryl boric acids under mild conditions, representing a low environmental impact and a non-toxic methodology. The chemoselectivity of the reaction was shown for the synthesis of bromo-substituted biaryls, which could have significant synthetic relevance.<sup>89</sup> 1,4-Dihydropyridines, representing an important class of N-heterocyclic scaffolds, could act as ligands for biological receptors in the field of medicine. A highly efficient, environmentally-friendly one-pot protocol was reported for their manufacture, including biologically active substrates in ethyl lactate under thermal and light mediated conditions (Scheme 23). Although a good isolated yield (75%) was obtained in ethyl lactate, it can be increased up to 92% by addition of water as a co-solvent.<sup>90</sup> The heterocyclic spirooxindole skeleton is of the utmost importance in organic and medicinal chemistry because of its potency across a wide spectrum of biological activities: these compounds have antifungal, antimicrobial, anti-tumor, anti-oxidant, anti-microbial, and anti-malarial effects, and can also serve as synthons for naturally occurring alkaloids and pharmaceutically important drug molecules. Excellent isolated yields (>88%) were achieved for



**Scheme 22** Cross-coupling reactions in a water/ethyl lactate mixture.



**Scheme 23** Synthesis of 1,4-dihydropyridines.





**Scheme 24** Synthesis of spiro[benzo[*f*]pyrrolo[2,1-*a*]isoindole-5,30-indoline]-20,6,11-trions.

spiro[benzo[*f*]pyrrolo[2,1-*a*]isoindole-5,30-indoline]-20,6,11-trions in both ethyl lactate and ethyl lactate water mixtures at room temperature over 1 h (Scheme 24).<sup>91</sup>

Alcohols represent a family of easily tuneable solvents *via* the variation in the number of polar and protic hydroxyl functional group(s) on the apolar and non-protic alkyl group(s). This property can be spectacularly demonstrated in the Shell Higher Olefin Process (SHOP), which manufactures higher  $\alpha$ -olefins from ethylene *via* controlled oligomerization (Scheme 25). While 1,4-butanediol serves the Ni-based catalyst containing phase, where the oligomerization takes place, the limited solubility of  $\alpha$ -olefins results in facile product separation.<sup>92</sup> It is important to note that the SHOP process was the first realization of an industrial biphasic catalytic system.

Fluorous solvents such as perfluorinated alkanes, dialkyl-ethers, and trialkylamines are extremely non-polar reaction media. Miscibility of these compounds, even with common organic solvents such as toluene, acetone, tetrahydrofuran, and alcohols is low at room temperature. Consequently, these liquids could easily form biphasic systems. The term “fluorous” was first introduced by Horváth in a seminal paper published in 1994,<sup>93</sup> as an analogue to the term aqueous, to emphasize the fact that one of the phases of the biphasic system is richer in fluorocarbons than the other. Fluorous biphasic systems (FBS) can be used in a huge variety of chemical transformations to immobilize catalysts. A typical fluorous catalyst system consists of a fluorous phase containing a preferentially fluorous soluble catalyst and a second product phase, which may be made up of any organic or non-organic solvent with limited solubility in the fluorous phase. The original image of the fluorous concept is shown in Fig. 2. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with a high number of carbon atoms that may contain other heteroatoms. The great potential of the fluorous-liquid/liquid concept for catalyst recovery was first demonstrated for the hydroformylation of olefins. The fluorous soluble P[CH<sub>2</sub>CH<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>]<sub>3</sub> modified Rh catalyst system is excellent for the hydroformylation of decene-1 at 100 °C under 11 bar



**Fig. 2** Original drawing of the fluorous biphasic concept for the catalytic conversion of substrates A and B to product P. Adapted from ref. 93. Copyright of The American Association for the Advancement of Science (1994).

syngas pressure (CO : H<sub>2</sub> = 1 : 1) in CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub> and the aldehydes can be easily separated from the fluorous catalyst, which was subsequently tested under semi-continuous and continuous conditions. The first investigation focused on the hydroformylation of decene-1 with the catalyst Rh[P[(CH<sub>2</sub>)<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>]<sub>3</sub>]. For nine consecutive reaction/separation cycles, a total turnover of more than 35 000 was achieved with a loss of 1.18 ppm of Rh per mol of undecanals. The same system was then tested under continuous hydroformylation of ethylene using FC-70, which allows the continuous removal of propanal at 110 °C. The long-term stability of the catalyst was found to be better than that of the classical Rh/PPh<sub>3</sub> catalyst, representing the first system which could be used for the hydroformylation of both low- and high-molecular weight olefins providing facile catalyst separation for both low and high molecular weight aldehydes.<sup>94</sup> After the successful introduction of “fluorous catalysis” several transition metal complexes bearing fluorous ligands were synthesized in collaboration with Gladysz including HRh(CO){P[CH<sub>2</sub>CH<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>]<sub>3</sub>}, the fluorous Wilkinson’s catalyst ClRh{P[CH<sub>2</sub>CH<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>]<sub>3</sub>},<sup>95</sup> the Ir-based fluorous Vaska complex ClIr(CO){P[CH<sub>2</sub>CH<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>]<sub>2</sub>},<sup>96</sup> and its rhodium analogue,<sup>97</sup> binuclear [Ru(μ-O<sub>2</sub>CCH<sub>3</sub>)(CO)<sub>2</sub>][P[CH<sub>2</sub>CH<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>]<sub>3</sub>]<sub>2</sub>,<sup>98</sup> fluorous porphyrins with Co, Fe, and Mn metal centers,<sup>99</sup> and fluorous cyclopentadienyl complexes with Mn, Re, Fe, and Co metal centers.<sup>100</sup> Since 1994, fluorous chemistry has become a well-established, individual area of chemistry, providing a complementary approach to other biphasic systems. In the case of need, the catalytic decomposition of perfluoroalkanes is available.<sup>101</sup> Overviews in the recent developments in fluorous chemistry have been published presenting excellent examples of its application.<sup>102–105</sup>

Organic carbonates, such as dimethyl carbonate (DMC), are excellent solvents for several catalytic transformations. Fischmeister demonstrated that DMC could be used as an environmentally-friendly alternative to conventional organic solvents (such as dichloromethane, benzene, toluene, chlorobenzene) used for the metathesis reaction. When 2<sup>nd</sup> generation Grubbs or Hoveyda catalyst (Scheme 26) mediated ring-closing metathesis (RCM) reactions of functionalized dienes (Scheme 22) were compared in CH<sub>2</sub>Cl<sub>2</sub> and DMC, almost iden-

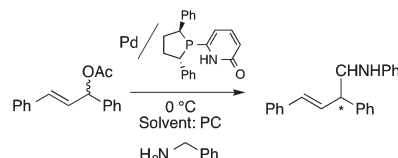


**Scheme 25** Oligomerization of ethylene (the SHOP-process).





Scheme 26 Ring-closing metathesis in DMC.



Scheme 29 Pd-Catalyzed asymmetric allylic alkylation using a chiral phosphine catalyst.

tical reaction profiles and isolated yields were achieved. The cross-metathesis of decene-1 and methyl acrylate also proceeded equally in DMC, yielding H<sub>17</sub>C<sub>7</sub>CH=CHCO<sub>2</sub>Me. It should be noted that sterically-hindered disubstituted olefins have been subjected to RCM, and outstanding product yields were achieved in DMC, due to the increased (90 °C) reaction temperature. As a subsequent development, the Hoveyda catalyst was immobilized on a silica or zirconia surface and tested in model RCM reactions and the re-use of the catalyst was demonstrated over several consecutive runs.<sup>106,107</sup> The same group utilized diethyl carbonate (DEC) as a replacement for conventional *N*-methyl-2-pyrrolidone in the direct functionalization of arene sp<sup>2</sup> C–H bonds by aryl halides. The catalytic system based on [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>/KOiv was found to be active in the selective arylation reaction of phenylpyridine at 80–120 °C depending on the type of chloroaromatic substrate used (Scheme 27).<sup>108</sup> DEC was also successfully utilized as a reaction medium for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate (in comparison with CH<sub>2</sub>Cl<sub>2</sub> as a conventional solvent) by Börner and co-workers (Scheme 28).<sup>109</sup> Using Me-phox as a ligand, no change in yield and enantiomeric excess was detected. The same group demonstrated the asymmetric allylic amination of 1,3-diphenyl-3-acetoxyprop-1-ene with benzyl amine in propylene carbonate (PC) at 0 °C (Scheme 29). Similarly, methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>) can be replaced by an eco-friendly solvent, resulting in a superior yield (91%) and enantioselectivity (57%).<sup>109</sup>



Scheme 27 Ru-Catalyzed C–H bond functionalization in DEC.



Scheme 28 Pd-Catalyzed asymmetric allylic alkylation in DEC.

Supercritical carbon dioxide (scCO<sub>2</sub>) should also be noticed as one of the frequently utilized alternative reaction media for chemical synthesis. It has a critical temperature *T*<sub>c</sub> = 31.0 °C, and critical pressure *p*<sub>c</sub> = 73.8 bar with a respective density of *d*<sub>c</sub> = 0.446 g mL<sup>−1</sup>. It can be used as a low cost and readily available solvent either by itself or in combination with other solvents such as hydrocarbons, ionic liquids, or fluorinated solvents. Due to its physical properties, no product contamination has to be considered in case of its accidental release into the immediate environment or even in final product separation. The latter allows the specific utilization of scCO<sub>2</sub> in the food and nutrient industry, in which the extraction of caffeine from coffee bean represents a long-term industrial application.<sup>110</sup> Over the last few decades, the successful introduction of scCO<sub>2</sub> as a solvent in chemical processes has been widely demonstrated from the laboratory to industrial scale involving dry cleaning processes and metal degreasing,<sup>111</sup> synthesis and catalysis,<sup>112,113</sup> and materials science.<sup>114</sup> Furthermore, in the pharmaceutical industry, where residual solvent traces are crucial and could result in serious health issues, the separation of enantiomers using scCO<sub>2</sub> could also offer a benign alternative to conventional resolution techniques.<sup>115</sup> For example, the separation of racemic ibuprofen that frequently uses model compounds by applying *in situ* diastereomeric salt formation between racemic ibuprofen and (*R*)-(1)-phenylethylamine, followed by its precipitation *via* a gas antisolvent method, resulted in up to 80% ee of (*S*)-ibuprofen.<sup>116,117</sup>

### Use of renewable feedstocks

Currently, more than 90% of the energy needs of mankind, as well as the production of carbon-based chemicals, are produced from resources originating from fossils. The exact date of the depletion of crude oil, the main carbon resource of the chemical industry, is very hard to estimate and has been the subject of active debate. In 2014, the estimated reserves of crude oil were calculated to be 1700.2 billion barrels, which is *ca.* 600 billion barrels more than the amount calculated 20 years ago. This value accounts for more than 50% of the reserves that were proven to be in the Middle East at the end of 2015.<sup>118</sup>

Despite this increase in the amount of crude oil, global efforts to reduce CO<sub>2</sub> emission according to the Kyoto Protocol, and the possible production of carbon-neutral end products have directed researchers' attention towards identifying and developing innovative solutions for the replacement of



fossil-based resources by renewable alternatives. The contribution of hydropower, wind, and photovoltaic energy<sup>119,120</sup> to our overall energy demand and utilization of carbon dioxide have emerged over *ca.* 30 years. For the chemical industry, the utilization of biomass as a readily and globally available feedstock has come into focus and has been proposed as a most promising alternative to the use of carbon resources.<sup>26,121–128</sup> Considering the increasing population of the Earth, the selection and consumption of appropriate resources have become controversial issues due to the dramatic increase in the use of edible resources. Thus, the production of energy and carbon-based chemicals from biomass cannot be seen to compete either directly or indirectly with food or feed production. On the other hand, this issue involves the availability or even an increase in the demand of land use, which gives the amount of soil (given in hectares) required to produce 1 ton of primary agricultural products. Obviously, the proper solution could be the vaporization of lignocellulosic rich waste streams,<sup>129</sup> because of their very similar composition.<sup>130</sup> A series of potential candidates obtained from carbohydrates, such as 5-HMF from cellulose, FAL from hemicellulose, as well as LA, 3-hydroxypropionic acid, furandicarboxylic and fumaric acids *etc.* was collected by Werpy and Petersen in 2004,<sup>131</sup> and updated by Bozell in 2010.<sup>124</sup> In 2008, GVL was also additionally proposed as a safe platform chemical by Horváth.<sup>30</sup>

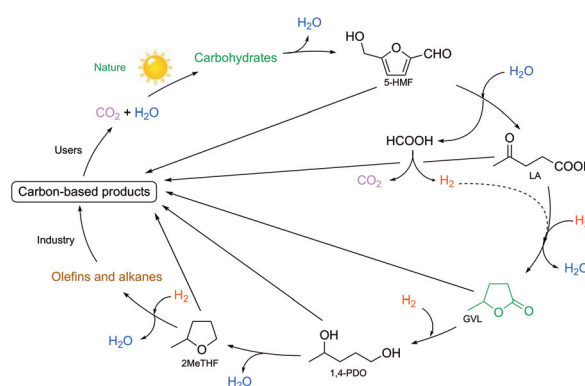
Although biomass could be an ideal alternative, its sustainable utilization primarily depends on whether we have enough resources to cover the increasing needs of fuels and chemicals. To improve the evaluation of biomass utilization from a sustainability point of view, Horváth and co-workers proposed a new definition of sustainability using two fundamental evolutionary principles and mechanisms of Nature as follows (i) “resources including energy should be used at a rate at which they can be replaced naturally” and (ii) “the generation of waste cannot be faster than the rate of their remediation”.<sup>132</sup> It should be emphasized that this novel approach addresses the changes in time (or the kinetics required to reach sustainable equilibria) and offered the opportunity to calculate the upper limits of sustainability per capita (or the parameters of sustainable equilibria). To calculate the sustainability of fuels (gasoline and jet fuels) and basic chemicals (ethylene, propylene, benzene, *etc.*) a new metric, the ethanol equivalent (EE) was introduced and used to calculate the land requirements of the biomass-based production of the corresponding products.<sup>132</sup> As a subsequent development of this theory, three indicators, *i.e.* the sustainability value of the resource replacement ( $SV_{rep}$ ), the sustainability value of the fate of the waste ( $SV_{waste}$ ), and the sustainability indicator ( $SUS_{ind}$ ) were defined as the sustainability metrics of carbon-based chemicals.<sup>133</sup> This methodology introduced by Horváth allows a calculation and comparison of the sustainability indexes of materials and processes relating to the chemical industry.

The first approach of the utilization of a complex biomass feed could be the “biorefinery concept”, which involves the integration of conversion processes to produce fuels, power, heat, and value-added chemicals by using up all of the carbon

atoms of the resource. However, due to the complexity of lignocellulosic material, this has only been partially realized by transformation of its carbohydrate content. As a novel concept in this huge research field, Horváth achieved the multistep catalytic conversion of carbohydrates to alkanes and alkenes involving (i) dehydration of sucrose to LA *via* 5-HMF in the presence of sulfuric acid at 140 °C; (ii) aqueous reduction of LA to obtain GVL using either TPPTS or a  $PBu_3$  modified Ru catalyst under a 70 bar pressure of  $H_2$  at 135–140 °C for 12 h and 8 h, respectively; (iii) hydrogenation of LA to GVL and 1,4-PDO in the presence of the catalyst  $[(\eta^6-C_6Me_6)Ru(bpy)(H_2O)][SO_4]$  and  $HCOONa$  under aqueous conditions at 70 °C for 18 h; (iv) hydrogenation of GVL to 2Me-THF using a  $Ru/PBu_3/NH_4PF_6$  catalyst system under a 75 bar pressure of  $H_2$  at 200 °C for 20 h; and (v) reduction of 2Me-THF to alkanes and alkenes by applying a  $Pt(acac)_3/CF_3SO_3H$  catalyst at a 75 bar pressure of  $H_2$  at 150 °C for 15 h. As a result, *ca.* 53%  $C_4$ -alkanes, 19%  $C_5$ -alkanes, 7%  $C_8$ -alkanes, and 6%  $C_9$ -alkanes were identified by NMR.<sup>34</sup> The multistep conversion is depicted in Scheme 30.

Recently, several production routes and successful applications of platform chemicals were demonstrated and numerous reviews have been published summarizing these results and innovations.<sup>26,121,123,134–137</sup> Thus, we provide selected examples regarding platform chemicals that are presented in Scheme 26.

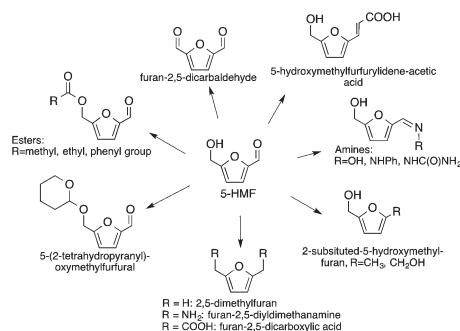
5-Hydroxymethylfurfural has been identified as a promising  $C_6$ -building block serving as a renewable alternative for polymers, pharmaceuticals, agrochemicals, flavors and fragrances, macro- and heterocycles, and natural products (Scheme 31).<sup>26,135</sup> It has also been proposed as a precursor for fuel components. Furan-2,5-dicarboxylic acid, that can be obtained by its oxidation, was also highlighted by the US Department of Energy as being a key bio-derived basic chemical that represents a starting point for the synthesis of several molecules, *i.e.* succinic acid, 2,5-furandicarboxylic acid dichloride, and 2,5-furandicarboxylic acid dimethyl ester. It is also a potential substitute for terephthalic or isophthalic acids



**Scheme 30** Multistep conversion of the carbohydrate content of biomass wastes. Modified with permission from ref. 34. Copyright of Springer (2008).







**Scheme 31** Chemicals derived from 5-HMF.

in the manufacture of polyamides, polyesters and polyurethanes.<sup>126</sup> It can also be applied as a cross-linking agent for poly(vinyl alcohol) in battery separators and as a component for foundry sand binders. Selective hydrogenation of 5-HMF leads to the formation of either 2,5-bis(hydroxymethyl)furan or 2,5-bis(hydroxymethyl)-tetrahydrofuran, which could be used in the manufacture of polyurethane foams or polyesters. The hydrogenolysis of 5-HMF results in the formation of 2,5-dimethylfuran, which has been targeted as a transportation fuel.

Levulinic acid has been identified as a non-toxic multi-purpose C<sub>5</sub> initial platform chemical<sup>26</sup> for the synthesis of functionalized C<sub>3</sub>–C<sub>6</sub> chemicals (Scheme 32). Its various ester derivatives may be used as blend components in fuels as well as also having significant potential as renewable replacements for kerosene as a home heating oil and as a fuel for the direct firing of gas turbines for electrical generation.<sup>138</sup> A Bisphenol-A analogue, diphenolic acid (4,4-bis-(4'-hydroxyphenyl)pentanoic acid) derivative of LA prepared by the reaction of LA with two equivalents of phenol could be a renewable substitute for the synthesis of polycarbonates, epoxy resins, and polyarylates.<sup>136</sup> LA also has numerous other uses, including applications in lubricants, adhesives and paints, while its sodium salt is used as an anti-freezing agent, and calcium levulinate can be applied orally or intravenously as a calcium ion carrier.<sup>139</sup>  $\delta$ -Aminolevulinic acid is a natural active ingredient in a series of environmentally benign, highly selective, broad-spectrum herbicides that can be used as insecticides.<sup>140,141</sup>



**Scheme 32** Chemicals derived from LA.

Gamma-valerolactone, a naturally occurring C<sub>5</sub>-cyclic ester in fruits and a frequently used food additive, was discussed above.

2-Methyltetrahydrofuran has been listed as a renewable fuel additive and a component of the alternative P-fuels, which can be used alone or may be mixed in any proportions with petroleum.<sup>142</sup> 2-MeTHF can be added in amount of up to 30 vol% with petroleum with no adverse effects on the performance, and engine modifications are not required. Vehicle tailpipe and evaporative emissions tests carried out by the Environmental Protection Agency revealed that the P-Series formulations reduced the ozone forming potential of the fuels and resulted in reduced emissions of non-methane hydrocarbons and total hydrocarbons: *ca.* 30% of those formed from the use of commercial reformulated gasoline. It has been also estimated that when biomass-based 2-MeTHF and EtOH are utilized, the full fuel-cycle greenhouse gas emission levels could be between 45 and 50% below the levels seen using reformulated gasoline. 2Me-THF could also be used as a renewable solvent, however, its ability to form peroxides has to be noted. Horváth showed that the peroxide number of 2Me-THF can reach 716 over 12 days, which actually means that it must be handled as a dangerous material.<sup>31</sup>

### Catalysis

The ninth amendment of Anastas and Warner to the reach goals of Green Chemistry, describes the use of catalytic reagents, which are superior to stoichiometric ones. By definition, a catalyst is a substance that accelerates a chemical reaction without being consumed; therefore, it can be recovered at the end of the process. Selective acceleration of a chemical process allows a reduction in the amount of byproducts, thus, chemical catalysis is a form of industrial metabolism.

Transition metal-assisted homogeneous catalysis offers a very efficient tool for the transformation of a huge variety of organic substrates over their heterogeneous counterparts. Their tunable and therefore significantly higher chemoselectivity, regioselectivity, enantioselectivity and milder operating conditions have to be emphasized. However, the catalyst separation and even recycling have been a great challenge and the subjects of recent research. Over the last few decades, several attractive solutions have been developed. In order to overcome the separation difficulties of homogeneous catalysts, several attractive solutions have been developed such as biphasic catalysis<sup>143</sup> or the heterogenization of homogeneous catalysts.<sup>144</sup> Among them, an elegant solution is the immobilization of homogeneous catalysts dissolved in a liquid phase on a solid carrier. The first stationary liquid phase catalyst (SLP, see Fig. 3), applied to the hydrogenation of arenes (benzene, toluene, *o*-xylene, and naphthalene), was reported by Horváth in 1991. The BF<sub>3</sub>·H<sub>2</sub>O–Pt catalyst was immobilized on CPG-240 or on clay.<sup>145</sup> A catalyst prepared from BF<sub>3</sub>·H<sub>2</sub>O and Pt(Cl)<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> was active in the reduction of a mixture of benzene and its alkyl-derivatives, such as toluene, *o*-xylene, and 1,2,4-trimethylbenzene under a 27.6 bar pressure of H<sub>2</sub> at



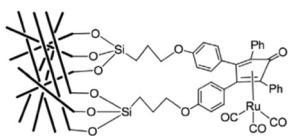


Fig. 3 A diagram showing supported liquid phase catalysis. Modified with permission from ref. 145. Copyright of John Wiley and Sons (1991).

22 °C. It was shown that the catalyst operated in the aqueous acid phase and that the solid did not chemically participate in the reaction. Recently, Horváth demonstrated the immobilization of a Shvo-type catalyst on silica using both covalent anchoring and sol-gel methods to prepare a recyclable transfer hydrogenation catalyst (Scheme 33).<sup>146</sup>

The Ruhrchemie/Rhône-Poulenc reaction offers the excellent recycling of a  $\text{HRh}(\text{CO})(\text{TPPTS})_3$  catalyst dissolved in water. The process is based on the significant differences between the high and low solubility of propylene and  $\text{C}_4$ -aldehydes, respectively, in the aqueous phase. However, it is an intrinsic characteristic of the hydroformylation reaction that the reaction rate declines upon an increase in the chain length of the olefin under similar conditions.<sup>147</sup> In the case of aqueous systems, it was suggested that the reaction under biphasic conditions with water-insoluble higher olefins was mass transfer limited.<sup>148</sup> This fact is attributed to the decreasing solubility of higher olefins in the aqueous catalyst solution, which correspondingly leads to low olefin concentrations and thus reduced reaction rates.<sup>149</sup> One of the most intriguing approaches for overcoming the solubility limitation is the immobilization of an aqueous solution of  $\text{HRh}(\text{CO})(\text{TPPTS})_3$  onto a high surface area hydrophilic silica support.<sup>150</sup> It was later shown by Horváth using *in situ* infrared (IR) spectroscopy that the SAP (Supported Aqueous Phase) catalyst lost water at higher temperatures, significantly lowering the amount of water available on the support as well as that of the hydrophilic support holding the water-soluble phosphines by hydrogen bonding of the hydrated sodium-sulphonate groups to the surface and that the actual catalytic reaction occurs in the organic phase (Fig. 4).

Biocatalysis offers an excellent tool for the manufacturing of primarily biologically active compounds that usually have one or more chiral center. This was recognized by pharma-



Scheme 33 A heterogenized Shvo-type catalyst. Modified with permission from ref. 146. Copyright of Elsevier (2017).

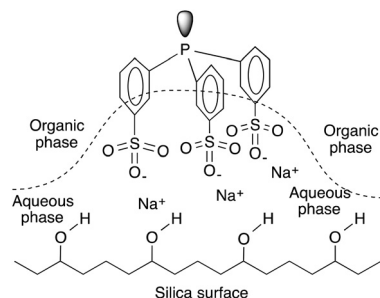
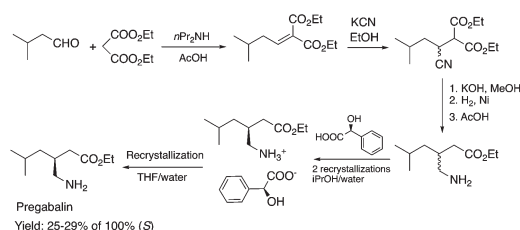


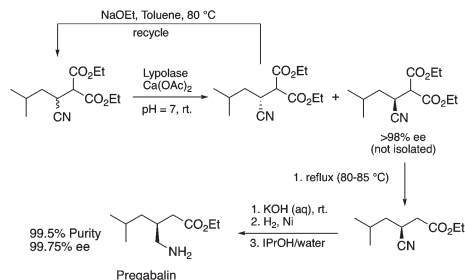
Fig. 4 Schematic representation of the immobilization of TPPTS on silica. Modified with permission from ref. 149. Copyright of Springer (1990).

ceutical companies that have integrated this green and sustainable methodology with traditional medicinal chemistry. There is no doubt that the modern pharmaceutical industry cannot be operated without biotechnology. While a large number of enzymes, the catalysts of biochemical transformations, have been known for a long time, protein and gene engineering has enabled the optimization or improvement of the efficiency of existing biocatalysts followed by their implementation into new biocatalytic transformations, which were previously unknown in Nature. Because of this possibility, applications, and recent achievements in the field of biocatalytic transformations have been widely reviewed.<sup>151–156</sup> Herein, we provide only selected examples for the benefit of biocatalytic conversion. In the pharmaceutical industry, the application of biocatalysis could reduce the number of synthesis steps required in the synthesis of products, as well as resulting in higher purities and product yields. For example, Pfizer have developed an efficient route for the synthesis of (*S*)-3-(aminomethyl)-5-methylhexanoic acid, Pregabalin, which is an antiepileptic drug used for central nervous system disorders. The original commercial synthesis route starts with a Knoevenagel condensation, followed by cyanation that results in a racemic mixture, hydrolysis, decarboxylation, and hydrogenation. A classical chiral resolution in the presence of (*S*)-(+)-mandelic acid was then applied to form a diastereomeric salt, which was separated by recrystallization in *i*PrOH/water. The pure ingredient is isolated after subsequent recrystallization from THF/water (Scheme 34).<sup>157</sup> Pfizer's eventual solution, based on the enzyme-catalyzed kinetic resolution hydrolysis of one of the esters of  $\beta$ -cyano-diester significantly reduced the amount of



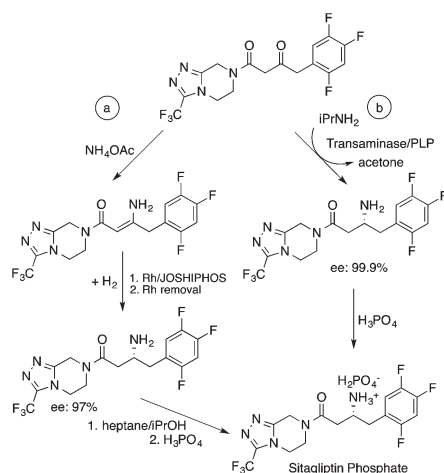
Scheme 34 Classical (first generation) synthesis of Pregabalin.<sup>157</sup>



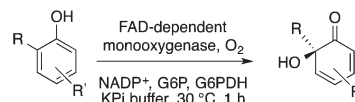


**Scheme 35** Enzymatic synthesis of Pregabalin.<sup>158</sup>

waste generated and increased the final yield of the target species (Scheme 35). This development resulted in the reduction of the E-factor of the process from 86 for the original process to 17 for the enzyme-based route. It has to be noted that the authors also reported a reduction in solvent use from 50 kg kg<sup>-1</sup> product to 6.2 kg kg<sup>-1</sup>.<sup>158</sup> The biocatalytic asymmetric synthesis of chiral amines that have opened is a very efficient and safe way to manufacture Sitagliptin, a treatment for type 2 diabetes, and can be highlighted as another excellent example of biocatalysis. Merck's process applies a transaminase enzyme for the amination of the pro-sitagliptine diketone precursor in the presence of iPrNH<sub>2</sub> (Scheme 36).<sup>159</sup> The process was made more environmentally friendly and industrially viable by avoiding the Rh/JOSIPHOS-catalyzed high-pressure hydrogenation step to result in a *ca.* 12% increase in the overall yield and *ca.* 50% increase in the total productivity. It should also be noted that the engineered transaminases also enabled access to chiral amines that heretofore could not be synthesized either enzymatically or chemically to yield chiral trifluoromethyl substituted and chiral pyrrolidine products. Narayan very recently reported the site- and enantioselective oxidative dearomatization of phenols, a chemical transformation that rapidly builds up in molecular complexity



**Scheme 36** Chemocatalytic (a) and biocatalytic (b) synthesis of Sitagliptin. Adapted with permission from ref. 159. Copyright of The American Association for the Advancement of Science (2010).



**Scheme 37** Oxidative dearomatization of phenols. A large variation of R and R' is presented in ref. 160.

from simple starting materials and cannot be accomplished with high selectivity using existing catalytic techniques (Scheme 37). Using enzymes from biosynthetic pathways, a method to produce a series of *ortho*-quinols from corresponding phenols was developed and additionally, the scalability and robustness of this novel multi-enzyme and chemo-enzymatic cascade method was demonstrated.<sup>160</sup>

Heterogeneous catalysis represents the heart of industrial catalysis. More than 95% of industrial chemical conversions involves catalysts, of which more than 90% are heterogeneous systems. Their heavy use is due to their robustness and easy separation from the product(s). While homogeneous systems exhibit high activity and selectivity, as mentioned above, heterogeneous ones have less selectivity and activity, and therefore can operate at a higher pressure and temperature. There is a huge number of applications of heterogeneous catalysis from basic academic research to large-scale industry. Their importance has been highlighted in recent reviews,<sup>161–163</sup> so therefore, it does not need to be reiterated herein. However, an industrially important heterogeneously catalyzed conversion of toluene to xylenes and benzene *via* a disproportionation reaction (STDP: Selective Toluene Disproportionation Process) should be noted as an excellent example of a “neat” heterogeneous transformation. The reaction is controlled by shape selectivity of the zeolite catalysts and yielded *p*-xylene in over 87%, with full conversion of toluene.<sup>164</sup> Despite the outstanding importance of heterogeneous catalysis in the chemical industry, due to the use of usually heavy and even toxic metals as catalysts, for instance copper chromite for the reduction of furfural to furfuryl alcohol, in the long term, biocatalysis seems to be more viable.

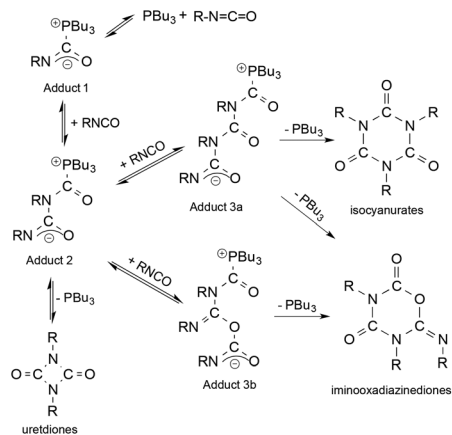
### *In situ* analysis

*In situ* analysis is one of the fundamental processes of life. For example, in the cells in our body the DNA is continuously attacked and damaged by external influences such as UV radiation and carcinogenic chemicals, including free radicals. During cell division, DNA is replicated, however, the cell recognizes and corrects errors that occur. This discovery was honoured by the Nobel Prize in Chemistry in 2015.<sup>165</sup> Without these mechanisms, life on Earth could not be possible. Biological evolution has had millions of years to develop precise *in situ* analytical processes to monitor biochemical transformations in living organisms. In chemical research, however, gathering molecular level information from chemical transformations, which is fundamentally important for a better understanding of reaction mechanisms, and the design of more selective catalysts that reduce the formation of by-pro-



ducts at the molecular level, has still been a great challenge. The application of *in situ* spectroscopy plays a key role in discovering the mechanism of reactions, involving the characterization of intermediates in real time. On the other hand, the verification of the existence of a species that was proposed to explain a known reactivity or even lead to the discovery of new intermediates could lead to different mechanistic explanations being revealed for well-known reactions. For example, the formyl cation  $[\text{HCO}]^+$  has long been proposed as a key species in the chemistry of CO under acidic conditions. However, its presence in solution was first established by IR and NMR spectroscopy by Horváth at Exxon in collaboration with Prof. John A. Gladysz in 1997. High-pressure IR measurements on a reaction mixture of  $\text{HF-SbF}_5$  and CO established the presence of  $[\text{HCO}]^+$  (Fig. 5) and additionally, the study also revealed additional equilibrium reactions in the superacidic environment.<sup>166</sup> A similar technique was used to monitor the carbonylation of  $\text{CH}_4$  with carbon monoxide in the superacids  $\text{HF/SbF}_5$  or  $\text{HSO}_3\text{F/SbF}_5$ . It was shown that the reaction leads to the exclusive and quantitative formation of the acylium ion  $[\text{CH}_3\text{CO}]^+[\text{SbF}_6]^-$  with the concomitant stoichiometric formation of  $\text{SbF}_3$ .<sup>167</sup>

Another excellent study focused on the chemistry of polyurethanes. These chemicals, manufactured from aliphatic isocyanates, represent an important class of high-performance materials. Accordingly, their efficient synthesis that takes place *via* catalytic processes is of utmost importance. Horváth and Richter investigated the mechanism of the tri-*n*-butylphosphine-catalyzed cyclooligomerization reactions of alkyl isocyanates (Scheme 38) and structurally characterized one of the key catalytic intermediates, Adduct 2, for the first time. The *in situ* IR and NMR measurements established the equilibrium formation of Adduct 1, which readily reacts with another isocyanate to yield Adduct 2. It can undergo a ring closure reaction



**Scheme 38** Proposed mechanism of the tri-*n*-butylphosphine-catalyzed oligomerization of isocyanates. Modified with permission from ref. 168. Copyright of Wiley-VCH (2005).

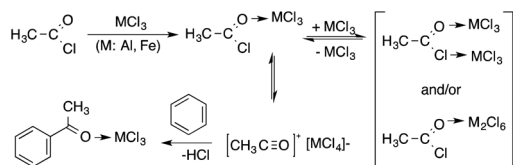
accompanied by the elimination of the catalyst  $\text{PBu}_3$  or act as an *O*- or *N*-nucleophile resulting in the formation of Adduct 3 and 4, respectively. While Adduct 3 was proposed to be responsible for the formation of isocyanurates, the ring closure of Adduct 4 resulted in the formation of iminooxadiazinediones.<sup>168</sup> This example can also be considered as an atom economic transformation under “neat” conditions.

Pioneering *in situ* analysis of the Friedel–Crafts acylation of aromatic compounds, a reaction that has been of utmost importance to the pharmaceutical industry, showed that no differences between reaction mechanisms could be observed, when conventional and toxic 1,2-dichloroethane was replaced by non-volatile 1-methyl-3-butylimidazolium chloride. The analysis established the presence of the key intermediates of the reaction, *i.e.* the acylium ion  $[\text{CH}_3\text{CO}]^+[\text{MCl}_4]^-$ .<sup>169</sup> The proposed mechanism is depicted in Scheme 39. In addition, it was revealed that replacing the hazardous solvent with an environmentally benign one had no influence on the reaction mechanism.

The *in situ* IR and NMR investigation of the mechanism of the pyridine modified cobalt-catalyzed hydromethoxy-carbonylation of 1,3-butadiene to methyl-3-pentenoate revealed that the initial step of the reaction sequence is the disproportionation of  $\text{Co}_2(\text{CO})_8$  to a  $[\text{CoPy}_6][\text{Co}(\text{CO})_4]_2$  salt, followed by its reaction with methanol to form acidic  $\text{HCo}(\text{CO})_4$ . Because the equilibrium between  $\text{HCo}(\text{CO})_4$  and  $[\text{MeOH}_2]$



**Fig. 5** IR spectra of (i)  $\text{HF-SbF}_5$ , (ii)  $\text{HF-SbF}_5 + ^{12}\text{CO}$ , and (iii)  $\text{HF-SbF}_5 + ^{13}\text{CO}$ . Modified with permission from ref. 166. Copyright of The American Association for the Advancement of Science (1997).



**Scheme 39** Proposed mechanism of the Friedel–Crafts acylation of benzene. Adapted with permission from ref. 169. Copyright of the Royal Society of Chemistry (2001).







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